Injection Site Reactions: Phlebitis can occur following the i.v. administration of paclitaxel. Extravasation during i.v. infusion can lead to edema, pain, erythema and induration. Occasionally extravasation can result in cellulitis. Skin discoloration can also occur. Recurrence of skin reaction at a site of previous extravasation following administration at a different site, so called "recall," has been reported rarely. A specific treatment of extravasation reactions is unknown, however treatment with s.c. injection of hyaluronidase diluted in saline has been shown to be effective in a mouse skin model.

Other: Mild and transient nail and skin changes have been observed. Radiation pneumonitis has been reported in patients who have received concurrent radiotherapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: There is not a known antidote for paclitaxel injection overdosage. The primary anticipated complications of overdosage would consist of bone marrow supperession, peripheral neurotoxicity and mucositis.

DOSAGE AND ADMINISTRATION: Note: Undiluted concentrate should not come in contact with plasticized PVC equipment. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel injection solutions should preferably be stored in glass or polypropylene bottles, or polypropylene or polyolefin plastic bags and administered through polyethylene-lined administration sets. Paclitaxel injection should be administered through an in-line filter with a microporous membrane not greater than 0.22 micron. Use of filter devices such as IVEX-2 filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP. All patients should be premedicated prior to Paclitaxel Injection administration in order to minimize severe hypersensitivity reactions. Premedication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 and 6 hours before paclitaxel injection, diphenhydramine 50 mg i.v. (or its equivalent) 30 to 60 minutes prior ot paclitaxel injection, and cimetidine (300 mg) or ranitidine (50 mg) i.v. 30 to 60 minutes preceding paclitaxel injection. Paclitaxel injection at a dose of 175 mg/m^2 administered i.v. over 3 hours every 3 weeks has been shown to be effective in patients with metastatic carcinoma of the ovary or breast who have failed standard therapy. Single courses of paclitaxel injection should not be repeated until the neutrophil count is at least 1500 cells/mm and the platelet count is at least 100 000 cells/mm. Patients who experience severe neutropenia (neutrophil <500 cells/mm or moderate to severe peripheral neuropathy during therapy should have the dosage reduced by 20% for subsequent courses.

Preparation and Administration Precautions: Paclitaxel injection is a cytotoxtic anticancer drug and, as with other potentially toxic compounds, caution should be taken in handling the product. The use of gloves is recommended. Following topical exposure, tingling, burning, and redness have been reported, If Paclitaxel injection solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If paclitaxel injection contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported.Paclitaxel injection at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks in combination with cisplatin 75 mg/m^2 is recommended for the primary treatment of patients with advanced carcinoma of the ovary. Paclitaxel injection should be administered before cisplatin when used in combination.

Preparation for I.V. Administration: Paclitaxel injectoin must be diluted prior to infusion. Paclitaxel injection should be diluted in Sodium Chloride Injection 0.9%, Dextrose Injection 5%, Dextrose 5% and Sodium Chloride 0.9% Injection, or Dextrose 5% in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/ml. The solutions are physically and chemically stable up to 27 hours at controlled room temperature. Upon preparation , solutions may show hazziness, which is attributed to the formulation vehicle. No significant loss in potency has been noted following simulated delivery of the solution through IV tubing which contains an in-line 0.22 micron filter. Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC (polyvinyl chloride) containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel injection solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used. As with all parenteral drug products. i.v. admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit.

SPECIAL INSTRUCTIONS: 1. Preparation of paclitaxel injection should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II), 2. Personnel preparing paclitaxel injection should wear gloves, safety glasses, disposable gowns and masks. 3. All needles, syringes, vials and other materials which have come in contact with paclitaxel injection should be segregated and incinerated at 1 000 °C or more. Intact vials should be returned to the distributor for destruction. Proper precautions should be taken in packaging these materials for transport. 4. Personnel regularly involved in the preparation and handling of paclitaxel injection should have bi-annual blood examinations.

AVAILABILITY AND STORAGE: Each mL of Paclitax injection contains: paclitaxel 6 mg. Nonmedicinal ingredients: Cremophor EL (polyethoxylated castor oil) and dehydrated alcohol. Vials of 5ml, 25ml, 50ml containing paclitaxel 30mg,150mg and 300mg respectively.

Store at 2 - 8 °C in refrigerator.

Manufactured by :

Pharmedic Laboratories (Pvt) Limited.

16 Km. Multan Road, Lahore - Pakistan

Phone : (92-42) 37511861 - 65, Fax : (92-42) 37511396

INJECTION

PACLITAX

(PACLITAXEL)

30mg, 150mg, 300mg

CAUTION:

Paclitaxel is a toxic product and should be administered only by or under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Patients receiving paclitaxel injection should be pre-treated using corticosteroids, antihistamines and H2 antagonists (for example dexamethasone, diphenhydramine and cimetidine or ranitidine) to minimize hypersensitivity reactions. Severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in patients receiving paclitaxel. These reactions are probably histamine mediated. One of these reactions was fatal in patient treated without premedication in a phase 1 study. Patients who experience severe hypersensitivity reactions to paclitaxel injection should not be re-challenged with the product.

ACTION AND CLINICAL PHARMACOLOGY: Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by the prevention of depolymerization.
In vitro paclitaxel has cytotoxic activity against a wide variety of both human and rodent tumor cell lines including leukemia, non-small cell lung carcinoma, small cell lung carcinoma, carcinoma of the colon, CNS tumors, melanoma, renal carcinoma, ovarian carcinoma and breast cancer.

Pharmacokinetics: The pharmacokinetics of paclitaxel have been evaluated in doses up to 300 mg/m^2 infused in a time period ranging from 3 to 24 hours. Following i.v. administration of paclitaxel, the drug exhibited a biphasic decline in plasma concentrations. The initial speedy decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. Values for mean terminal phase half-life, total body clearance, and apparent volume of distribution at steady state were determined following doses of 135 and 175 mg/m^2 administered as 3 and 24 hour infusions. Mean terminal half-life ranged from 3 to 52.7 hours. Total body clearance ranged from 11.6 to 24 L/h/m^2. The mean steady state volume of distribution ranged from 198 to 688 L/m^2 indicating extensive extravascular distribution and/ or tissue binding of paclitaxel. Mean terminal half-life was estimated at 9.9 hours after 3-hour infusions at 175 mg/m^2. Mean total body clearance was 12.4 L/h/m^2. There was no evidence of accumulation of drug with multiple treatment courses. There was minimal variability in systemic drug exposure for successive course of treatment as measured by AUC.
The pharmacokinetics of paclitaxel are nonlinear, this is most easily seen in patients where high plasma cohcentratoins are achieved and may be due to saturable processes in distribution and elimination/metabolism.
There are large disproportional increases in C_{max} and AUC with increased dose and an apparent dose-related decrease in total body clearance.
Paclitaxel is 89% or more bound to plasma protein in vitro.
The disposition of paclitaxel has not been fully determined in humans. After i.v. administration of paclitaxel mean values for cumulative urinary recovery of unchanged drug ranged from 1.3 to 12.7% of the dose, indicating significant non-renal clearance. The principal metabolites are hydroxylates isolated from bile. About 20% of an administered dose was recovered in bile as the parent compound and metabolites, in 1 patient in the 24 hours following treatment. Disposition of paclitaxel may be primarily hepatic metabolism and biliary clearance. The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated. The clearance of paclitaxel was not affected by cimetidine pre-treatment. Ketoconazole may inhibit the metabolism of paclitaxel based upon preliminary animal/ex vivo data. Similarly, there are preliminary reports which suggest that plasma levels of doxorubicin and its active metabolite doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination. The mechanism for this interaction is unknown and the pharmacodynamic consequences of this interaction are unclear.

INDICATIONS AND CLINICAL USES: For the treatment of carcinoma of ovary or breast, alone or in combination and in advanced non small cell lung cancer, has also been tried in other malignancies including tumor of the head and neck, prostate and kaposi's sarcoma.

Ovarian Carcinoma: First line therapy in combination with other chemotherapeutic agents; second line therapy for metastatic carcinoma of the ovary after failure of standard therapy.

Breast Carcinoma: Second line treatment of metastatic carcinoma of the breast after failure of standard therapy.

CONTRA INDICATIONS: Patients who have history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil). Paclitaxel injection should not be used in patients with severe baseline neutropenia, for example, less than 1500 cells/mm.

WARNINGS IN CLINICAL STATES: Paclitaxel injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Paclitaxel injection should be given as a diluted infusion. Patients receiving the product should be premedicated with corticosteroids, antihistamines, and H2 antagonists (such as dexamethasone, diphenhydramine, and cimetidine or ranitidine) to minimize hypersensitivity reactions. Severe hypersensitivity reactions including dyspnea, flushing, chest pain, tachycardia, hypotension requiring treatment, angioedema, and generalized urticaria have occurred in patients receiving paclitaxel by i.v. administration. These reactions are probably histamine mediated. One of these reactions resulted in the death of patient treated without premedication in a Phase I study. Infusion should be discontinued immediately if a patient experiences

a severe hypersensitivity reaction to paclitaxel injection. The patients should not be given paclitaxel injection again. Paclitaxel injection should not be administered to patients with baseline neutrophil counts below 1500 cells/mm. Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Frequent monitoring of blood counts should be instituted during treatment. Patients should not be retreated with subsequent cycles of paclitaxel injection until neutrophils recover to a level above 1500 cells/mm and platelets recover to a level above 100 000 cells/mm.

Severe cardiac conduction abnormalities have been rarely reported during therapy with paclitaxel, administered i.v; if patients develop significant conduction abnormalities, then appropriate therapy should be instituted and continuous ECG monitoring should be performed during subsequent therapy.
Pregnancy: Paclitaxel injection may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant during therapy. Paclitaxel was shown to be embryo and feto-toxic in rabbits and to decrease fertility in rats.

Lactation: Paclitaxel injection should not be administered to mothers who are nursing.

PRECAUTIONS: Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. To minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel injection should preferably be stored in glass or polypropylene bottles, or polypropylene or polyolefin plastic bags and administered through polyethylene-lined administration sets.

DRUG INTERACTIONS: In a Phase I trial in which paclitaxel (24 hour infusion) and cisplatin (1 mg/min infusion) were administered as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (paclitaxel before cisplatin). When paclitaxel is administered before cisplatin, then the safety profile of paclitaxel is similar to that for single-agent use. Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin. Therefore, when used in combination, paclitaxel injection should be administered before cisplatin. Preliminary animal/ex vivo data indicate that ketoconazole may inhibit the metabolism of paclitaxel. Caution should be observed in the treatment of patients receiving ketoconazole when undergoing paclitaxel therapy. There are preliminary reports that suggest that plasma levels of doxorubicin and its active metabolite doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination.

Hematology: Paclitaxel injection should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm. In order to monitor the occurrences of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving the drug. Patients should not be retreated with paclitaxel injection until neutrophil recover to a level greater than 1500 cells/mm and platelets recover to a level greater than 100 000 cells/mm. In the case of severe neutropenia (<500 cells/mm during therapy, a 20% reduction in dose for subsequent courses therapy is recommended.

Hypersensitivity reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL should not be treated with paclitaxel injection. Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of paclitaxel injection and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be given paclitaxel injection again.

Cardiovascular: Hypotension and bradycardia, usually asymptomatic, can occur during administration of paclitaxel injection that generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of infusion, is recommended. Continuous cardiac monitoring is not required except for patients who develop serious conduction abnormalities.

Nervous System: Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual. Moderate to severe neuropathy requires a dose reduction of 20% for all later courses of paclitaxel injection.

Paclitaxel injection contains dehydrated alcohol; the possible CNS and other effects of alcohol should be considered.

Hepatic: There is no evidence of increased toxicity of paclitaxel when administered as a 3-hour infusion to patients with mildly abnormal liver function. No data is available for patients with severe baseline cholestasis. When paclitaxel is given as a 24-hour infusion to patients with moderate to severe hepatic impairment, increased myelosuppression may be observed compared to patients with mildly elevated liver function tests.

ADVERSE REACTIONS: The incidence of adverse reactions are derived from 10 clinical trials in carcinoma of the ovary and of the breast involving 812 patients treated with paclitaxel at doses ranging from 135 to 300 mg/m^2 day and schedules of 3 or 24 hours.
The safety profile has been evaluated from a large randomized trial (paclitaxel 135 mg/m^2 over 24 hours with cisplatin75 mg/m^2 versus cyclophosphamide/cisplatin) which included 410 patients, 196 of whom received paclitaxel. Use of paclitaxel with platinum agents has not resulted in any clinically significant changes to the safety profile of the product when used at the recommended dosage.
Summary of 3-hour Infusion data at a dose of 175 mg/m^2. Unless otherwise stated, the following safety data relate to 62 patients with ovarian cancer and 119 patients with breast cancer treated at a dose of 175 mg/m^2 and a 3-hour infusion schedule,

in phase III clinical trials. All patients were premedicated to minimize hypersensitivity reactions. Data from these clinical trials demonstrate that paclitaxel administered at this dose and schedule is well tolerated. Bone marrow suppression and peripheral neuropathy were the principle dose related adverse reactions. Further, as compared to a 24-hour infusion schedule, the incidence of neutropenia was less common when paclitaxel was administered as a 3-hour infusion. Neutropenia was generally rapidly reversible and did not become worse with cumulative exposure. Repeated exposure increases the frequency of neurologic symptoms.
None of the observed toxicities were influenced by age.

Hematologic: The most frequent undesirable effect of paclitaxel was bone marrow suppression. Severe neutropenia (<500 cells/mm occurred in 27% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for 7 days or more. Neutropenia was not more frequent or severe in patients who received prior radiation therapy, nor did it appear to be affected by treatment duration or cumulative exposure. 18% of patients had an infectious episode, all non fatal. Although severe septic episodes associated with severe neutropenia attributable to paclitaxel were reported in early clinical trials, no severe infections or septic episodes were seen at the recommended dose and infusion schedule. There were 5 fatal septic episodes associated with severe neutropenia attributable to paclitaxel in the overall 812 patient database.
Thrombocytopenia with platelet counts <100 000 cells/mm was reported in 6% of patients. Thrombocytopenia with platelet counts <50 000 cells/mm was reported in 1% of patients. Severe thrombocytopenia (<50 000 cells/mm) was observed during the first 2 courses only. Bleeding episodes occurred in 9% of patients; no patient needed platelet transfusion.
Anemia was seen in 62% patients, but was severe (Hb<8 g/dL) in only 6% of patients. Incidence and severity of anemia are associated with baseline hemoglobin status Red cell transfusion were required in 13% of patients (6% of those with normal baseline hemoglobin levels).

Hypersensitivity Reactions: Severe hypersensitivity reactions occurred in 1% of patients even with premedication. These reactions occurred generally in early treatment courses and within the first hour of infusion. Dyspnea, flushing, chest pain and tachycardia were the most frequent signs and symptoms.
The dosage and schedule had no effect on the frequency of hypersensitivity reactions which occurred in 21% of courses where patients were given the recommended dose at the recommended schedule. The majority of reactions were minor. The most frequent were flushing (28%), rash (14%), and hypotension (3%).

Cardiovascular: During infusion of paclitaxel, hypotension and bradycardia were experienced by 24% and 4% of patients, respectively, and did not usually occur during the same course; the majority of episodes were asymptomatic and did not require treatment. One patient experienced transient hypertension during the second paclitaxel cycle. In addition, 2 patients experienced severe cardiovascular events (tachycardia and thrombophlebitis), possibly related to paclitaxel. None of these patients required discontinuation of treatment. In the same studies at lower dose or longer infusion, 3 severe cardiovascular events (atrioventricular (AV) block, syncope and hypotension associated with coronary stenosis resulting in death) possibly related to paclitaxel administration were reported. Ten severe cardiovascular events occurred which included cardiac rhythm disturbance and syncope among the 812 patients. An abnormal ECG occurred in 13% of patients during the clinical trials at a dosage of 175 mg/m^2 and a 3-hour infusion schedule. Some patients (8%) with a normal ECG prior to study entry developed an abnormal tracing during the study. Of the 812 patients, the most frequently reported ECG changes were nonspecific repolarization abnormalities, sinus tachycardia and premature beats. In most cases, there was no clear relationship between the administration of paclitaxel and ECG changes; these changes were of no, or minimal, clinical relevance. Since the above summary, cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other prior chemotherapy, especially anthracyclines.

Neurologic: Peripheral neuropathy, mainly manifested by paresthesia, affected 64% of patients, but was severe in only 4% of patients. Neurologic symptoms can occur following the first course and can worsen with increased exposure to paclitaxel. Peripheral neuropathy was the cause of drug discontinuation in 3 cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy. Rare neurologic events include grand mal seizures and encephalopathy. Reports of motor neuropathy with resultant minor distal weakness and autonomic neuropathy resulting in paralytic ileus and orthostatic hypotension have also been observed. Optic nerve and/or visual disturbance (scintillation scotomata) have also been reported, especially in patients who have received higher doses than recommended. These effects have generally been reversible.

Arthralgia/Myalgia: Arthralgia or myalgia affected 54% of patients and was severe in 12% of patients. The symptoms usually were pain in the large joints of the arms and legs and were transient occurring 2 to 3 days after administration and resolving within a few days.

Alopecia: Alopecia was observed in nearly all patients.

Gastrointestinal: Gastrointestinal side effects were usually mild to moderate: nausea/vomiting (44%), diarrhea (25%) and mucositis (20%) were reported. Other gastrointestinal events included anorexia (25%), constipation (18%) and intestinal obstruction (4%). Neutropenic enterocolitis, bowel obstruction/perforation and ischemic colitis and pancreatitis have occurred.

Hepatic: In patients with normal baseline liver function, 4% had elevated bilirubin, 18% had elevated alkaline phosphatase, and 18% had elevated AST. Severe elevations (>5x normal values) of bilirubin, alkaline phosphatase or AST were seen in 1%, 5% and 5% of patients, respectively. There have been rare reports of hepatic necrosis and hepatic encephalopathy leading to death.